

[Docket No. 98D-0077]

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Dockets Management Branch (HFD-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

September 10, 1999

Dear Sir/Madam:

The following comments are submitted by Roche in response to issues raised at the FDA OA guidelines meeting of July 1999 and the draft Guidance for Industry - Clinical Development Programs for Drug, Devices, and Biological Products Intended for the Treatment of Osteoarthritis (OA). We have taken the opportunity to review this document in light of our products in development for this disease state.

USE OF PRECLINICAL MODELS

Section II of the draft guidance document suggests that it would be useful to test compounds in models that are predictive of the risk benefit ratios to be expected in human OA. We would like to point out that the currently available animal models are usually associated with destabilization of the joint e.g. developmental loosening of the cruciates in the STR-ORT mice and Hartley guinea pigs, or mechanical destabilization in the rabbit meniscectomy model and the Pond-Nuki dog. Further, most of these models occur in younger animals in which the skeleton is still actively growing and in joints that have lower weight bearing loads compared to humans. Thus, the "predictability" of an animal model can only be defined retrospectively after the compound has been proven efficacious in a human clinical trial. We agree that these models are useful in approximating target plasma levels for the human trials. However, given differences in plasma protein binding and differences in the K_i of animal and human target receptors or enzymes, the target plasma levels should be considered a first order approximation.

Paragraph four of Section II suggests the studying of toxicity in the animal efficacy model. While this is an interesting suggestion, this raises a number of issues. First, efficacy studies are not usually run as GLP studies whereas toxicology studies are. Second, some of the models are in species rarely used for toxicology e.g., guinea pigs. Finally, the dosing requirements, tissue sampling, clinical chemistry etc., are different between toxicology and efficacy studies. Thus the suggestion to use the efficacy models as toxicity models raises many questions:

- Would the studies have to be conducted under GLP?
- Would two species of normal animals also be required?
- What advantages of using the efficacy species would be expected to occur?
- How should the lesioned areas be sampled to generate appropriate data? (It is hard to conceive of a joint-lesion effect on the major organs, like liver and kidney, that are targets of drug toxicity.)
- Have the models themselves been adequately characterized for 6-12 months so that the histology of the lesioned joints could be interpreted as showing toxicity rather than a normal consequence of the disease process or of aging? (This is particularly problematic in outbred species such as dogs.)
- If the metabolic breakdown of the compound in the efficacy species is different from that anticipated in humans, would data gathered in the efficacy species be less meaningful?

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The animal models represent a challenging area that the industry will continue to explore. Mechanistic studies are compromised by the youth of many of the animals in the models. In these young animals, the entire structure of the joint changes because of both growth and lesions over time, and as a result, the quantitation of structural features such as articular cartilage becomes extremely complicated. Further, the articular cartilage is thin in the small animals and therefore difficult to be measured accurately by MRI or other imaging modalities.

The measurement of biochemical markers is also complicated by the animals' growth, a situation that is similarly seen in man. For example, in man, there are high levels of collagen type II breakdown products in the urine of children, and the levels decrease only after growth plate closure. Rodents, on the other hand, have high levels of the same markers for most of their lives since some of their growth plates never close. While biochemical markers need to be tested in the animal models, their ultimate utility will be proven in man. At the present time, the decision to advance a compound into human trials cannot be predicted from results obtained with biochemical markers in animal models.

PRODUCT DEVELOPMENT

With regard to issues related to the pathogenesis, epidemiology, and clinical progression of OA, there are many questions pertaining to the disease which will be elucidated as we gather further information and develop methods to evaluate this disease. As we progress, we must apply the knowledge we have and test new hypotheses that in the course of time may or may not be proven to be true.

Morbidity in OA takes the form of pain, functional decline in ambulation, the use of specific joints, loss of income, loss of leisure time activities, and affects on personal perceptions of oneself, which can manifest as social withdrawal and depression. Therefore, in this context, it is worthwhile to treat OA from the perspective of the immediate clinical signs and symptoms and the progression of the disease.

In the development of drugs/devices for OA, we will coordinately determine if a therapy appears to be working based on its proposed mechanism and be able to evaluate if there are subgroups that benefit most or least to the therapy. In this context, subsequent trials and research can broaden the knowledge we gain while at the same time provide the therapeutic tools to ask the questions that could not be answered at this time. As the field progresses, (as we have seen discussed at the guidelines meeting), additional tools in outcome measures and surrogates should allow for further developments in the field of OA.

OSTEOARTHRITIS MEASUREMENTS

At this time, the tools that have best been characterized, and that have applicability to large clinical trials for setting the duration of treatment and the size of the population under study, are radiographic. For the moment, the medial joint space width of the knee appears to be furthest along of the current methods with regard to known rate of progression, performance of the technique, and validity within trials. Other methods are being sought, and are likely to supplant this method. But until that occurs, then the measurement of structure for OA appears to be best addressed by the aforementioned method. Hip OA radiographic scores are not as far advanced at this time but may be on equal scale in the near future. Therefore, currently knee medial joint space appears to be the preferred outcome measure for structure for OA. Since there is evidence that osteophytes may be important in OA, then they should be scored as well, since there are reliable atlases for standardizing their evaluation.

The joint, as well as other tissues, has a finite number of ways to respond to the environment and to injury. In the context of OA, whether the insult is from primary OA, trauma, or secondary OA, the cardinal findings of pain, effusion, crepitus, osteophytes, bony sclerosis, cartilage loss and geodes still persist in all joints that develop OA. The major differences are the amount of force loading in joints such as the lower extremities and upper extremities. To this end, therapies that demonstrate effects in an OA joint, especially if reproduced in a small joint such as a DIP/PIP/CMC and a large joint such as a hip or knee, are likely to at least be generally applicable to the OA population studied (e.g., primary OA) as opposed to only the specific joints studied.

The issue of evaluating clinical benefit has been addressed in a number of different ways. First, immediate clinical effects may not be seen with therapies that address structure. Their analysis may need to be deferred until such time that there is sufficient difference in structural progression before a formal analysis of such benefits takes place. This is not to say that early (within weeks to months) clinical benefit can not be sought in the early part of a development program, but if initial evaluations at early time points do not show clinical effect, then pursuing demonstrating an early effect for later trials would appear unwarranted.

Second, with regard to clinical benefit, evaluation of the use of assistive devices, rescue medications, physical therapy, alternative medications, topical analgesics, etc has been promulgated. During the conduct of a trial, one may attempt to address one or more of these issues in a rationale and orderly fashion. However, the final outcome often still has a great deal of variability in the actual practice of monitoring and documenting any of these confounders. Attempts at being rigid with the follow-up and evaluation often leads to significant increase in the complexity of the trial program and problems, including resistance, by both investigators and patients. In the final balance of what is achievable and useful, the most pragmatic approach appears to be by minimization of the confounders, and/or inclusion of them for the analysis.

OSTEOARTHRITIS CLAIMS

The degree of clinical benefit, and indeed the amount of benefit from protecting or repairing the osteoarthritic joint, needs to be sufficient to be “clinically meaningful” but not set so high that the first generation of disease modifying agents may fail. Given the uncertainties we have with OA with regard to disease progression, patient subsets that progress, measurements of effects, etc., the trials will certainly have design elements that are found not to be optimal when view retrospectively in the coming years. To this end, we may not be able to demonstrate the maximum benefit of any drug or therapy.

Therefore, consistent with what we have developed in the rheumatoid arthritis area, we would submit that an improvement of 20% in either clinical or structural benefit (or rate of decline in structure) is both clinically meaningful and achievable with our current trial designs, potential therapies and knowledge. As the field progresses, just as in RA, we could expect new therapies to meet or exceed what is achieved with the first generation of structurally beneficial therapies.

In viewing disease modifying agents that slow the progression of a disease that can take decades to progress, and that occurs often in older populations, the immediate change, or lack of change, in joint space is not the issue. It was discussed if 1 mm or so in joint space has any clinical significance. Instead, one could put forward that if a patient, age 55 years, has a reduced joint space of 4 mm and an average rate of progression of 0.2 mm/year, that the patient could have bone on bone in that area of the joint in 20 years. With a 30% reduction in that rate, the same event would occur at age 85 or 30 years later. Since bone on bone is not a desirable outcome, there is benefit to the patient in the long term, similar to what is argued for hypertension treatment with reduction in stroke, congestive heart failure and renal failure.

TRIAL DESIGN AND ANALYSES

From a statistical analysis point of view, Roche does not believe that research in OA differs from other diseases. We therefore propose that adjustments for multiple comparisons with regard to secondary endpoints (e.g. pain and function) and handling of missing data should be addressed in accordance with the ICH Guidance on Statistical Principles.

TREATMENT OF SYMPTOMS: PAIN AND FUNCTION

On another area of the guideline, there is an effort to have imaging studies done for agents that are purely for signs and symptoms to ensure that there is no deleterious effect on the joint of these agents. We disagree with this point - if there is no mechanistic, in vitro, or animal evidence of a negative effect on the joint, then there is reasonable basis not to pursue this in the clinic. There are several reasons for this:

1. The size of symptom-modifying study is insufficient to detect meaningful differences between groups for structural differences.
2. Symptom-modifying studies involve patients with a larger range of pathology, including those that are too severe to be evaluated effectively by imaging.
3. In order to use imaging to study patients we must reduce the joint severity of the population to be studied in a symptom modifying trial. By placing an upper limit on the severity of the joint disease, we limit the breadth of the patient population studied. The result is that the studied patients are less representative of the population to be treated and limits the knowledge of how the drug works in the more severe patients.
4. Proper imaging technique requires substantial site training, quality assurance measures, and central reading by trained experts, all of which substantially increase trial complexity, costs, and reduce the potential number of sites that can participate.
5. Patients will be unnecessarily subjected to imaging procedures that have little likelihood of having utility in demonstrating an effect.
6. "No deleterious effect" of a drug has not been clearly defined. In general, for a study to establish clinical benefit in signs and symptoms, the study duration is shorter than one that establishes structural outcome claims. Consequently, any deleterious effect may not be seen after the relatively short treatment duration unless the deterioration is large. Further to complicate the ability to determine the deleterious effect of a drug is the inherent error rate of the radiographic measurement technique.

NON-SIGNAL JOINTS

In the area of non-signal joints, patient and physician global evaluations of how the patients' arthritis affects them should help with understanding the general effect of the arthritis on the patient. The studied joints will require the intense evaluation from physical exam, imaging, questionnaires and other measures of efficacy. Additional measures to capture the non-signal joints will produce both patient and physician fatigue in running through too many evaluations, resulting in poor performance of all measures. In addition, general measures of function, such as the SF36, are likely to capture the effects of non-signal joints in sections such as bodily pain.

If you have any questions or comments regarding this document, please do not hesitate to contact the undersigned.

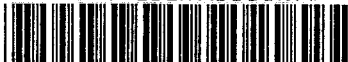
Sincerely,

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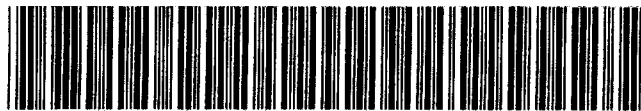
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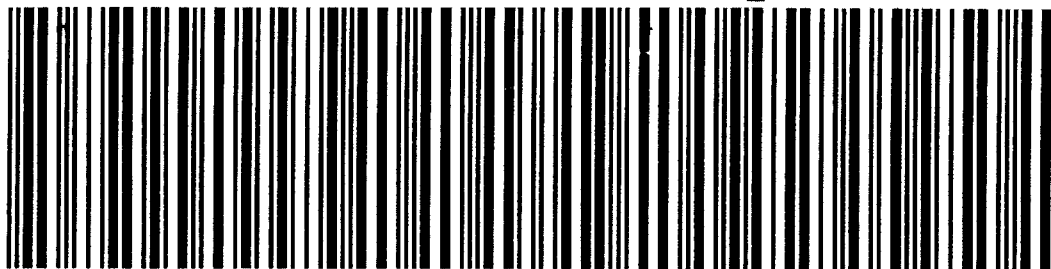
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